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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/673,707	01/11/2001	Ira H. Pastan	15280-3561US	3958

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Laurence J Hyman
Townsend & Townsend & Crew
8th Floor
Two Embarcadero Center
San Francisco, CA 94111-3834

EXAMINER	
ZEMAN, ROBERT A	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 10/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/673,707	**Applicant(s)** PASTAN ET AL.	
	Examiner Robert A. Zeman	**Art Unit** 1645	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 19 September 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *19 September 2005*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-11,52-58 and 68-78*.
   Claim(s) withdrawn from consideration: *19-24, 59-67 and 79-103*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

H.C

Continuation of 3. NOTE: miminally the proposed amendments require a new sequence search. Moreover, the scope of the claims have changed requiring new considerations.

DETAILED ACTION

The amendment after final rejection filed on 9-19-2005 has not been entered as they raise new issues requiring additional searching and considerations.

Claims 1-11, 19-24 and 52-103 are remain pending. Claims 19-24, 59-67 and 79-103 remain withdrawn from consideration as being drawn to non-elected inventions. Claims 1-11, 52-58 and 68-78 are currently under examination.

Applicant's arguments are predicated in part on amendments not made of record and hence are deemed non-persuasive. Those arguments not predicated on said amendments are addressed below.

Objections Maintained

The objection to the specification for referring to U.S. patent Applications that have since been issued is maintained. Applicant's arguments are based on amendments not of record.

The objection to the specification for disclosing that SEQ ID NO:1 is the sequence of both the intact 3b3 antibody and a 3b3(Fv) is maintained for reasons of record. Applicant's arguments are based on amendments not of record.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 8, 10, 55-56, 58, 74, 76 and 78 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained for reasons of record. Applicant's arguments are based on amendments not of record.

As outlined previously, the specification, contrary to Applicant's assertion does not explicitly define what sequences and linkers comprise either 3b3(Fv) or 3B3(dsFv). Both are deemed to be a unique singular entity comprising a V_H and a V_L sequence and a specific linker (if one was used). Applicant argues that the specification discloses the use of SEQ ID NO:1 and SEQ ID NO:2 in conjunction with an *exemplar* linker. The fact that the linker, as pointed out by Applicant, is variable, there is no **unique** sequence associated with the identifier 3b3(Fv).

With regard to Point 3, while the skilled artisan would be able to form disulfide-stabilized Fvs, there is no specific disclosure as to which amino acids in the 3B3 antibody need to be replaced with cysteines when forming the 3B3(dsFv). Consequently, the specific sequence associated either both 3b3(Fv) or 3B3(dsFv) is not known.

As stated previously, since it is apparent that antibodies 3b3(Fv) and 3B3(dsFv) as well as immunotoxins 3B3(Fv)-PE38 and 3B3(dsFv)-PE38 are required in order to practice the invention. The deposit of biological material is considered by the Examiner to be necessary for the enablement of the current invention (see 37 CRF 1.808(a)). The rejected claims all recite said biological material in a manner suggesting they each constitute a single entity. Since the specification provides no sequences for said material and one of skill in the art would not be able

to discern what V_H and V_L sequences of the 3B3 antibody are incorporated into the claimed 3B3(Fv) or 3B3(dsFv), deposit of the aforementioned biological material is required.

If the deposit is made under terms of the Budapest Treaty, then an affidavit or declaration by Applicants or person(s) associated with the patent owner (assignee) who is in a position to make such assurances; or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty *and* that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit, or declaration by Applicants or person(s) associated with the patent owner (assignee) who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the following criteria have been met:

1) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

2) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent; and

3) the deposits will be maintained for a term of at least thirty (30) years from the date of the deposit or for the enforceable life of the patent or for a period of at least five (5) years after the most recent request for the furnishing of a sample of the deposited material, whichever is longest; and

4) a viability statement in accordance with the provisions of 37 CFR 1.807; and

5) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 CRF 1.809(d) should be added to the specification. See 37 CFR 1.803 – 1.809 for additional explanation of these requirements.

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 1-6, 8-9, 11, 52-55,57, 68-72 and 74-77 under 35 U.S.C. 103(a) as obvious over Matsushita et al. (Aids Research and Human Retroviruses Vol. 6 No. 2, 1990, pages 193-203) in view of Barbas et al. (PNAS Vol. 91, 1994, pages 3809-3813 – IDS-5) and Pastan et al. (U.S. Patent 5,458,878 – IDS-5) is maintained for reasons of record.

Applicant argues:

1: Developments in the art after the date of Matsushita's publication would destroy the *prima facie* case of obviousness outlined in the rejection.

Applicant's arguments have been fully considered and deemed non-persuasive.

Applicant's arguments are predicated on references that are not germane to the instant invention.

The instant invention is drawn to immunotoxins comprising a cytotoxin (e.g. PE38) attached to an anti-gp120 antibody (e.g. 3B3) having the binding specificity of 3B3. Said antibody is a dsFv. The instant invention is also drawn to kits and compositions comprising said immunotoxins.

The Ramachandran et al. reference is drawn to CD4-PE40 immunotoxins that are not analogous to the instant invention as they do not target only infected cells. Hence any "results" based on the Application of said immunotoxin would not have any bearing on the perceived efficacy of immunotoxin based on the combination of the cited references which target only infected cells.

The Davey et al. reference is drawn to sCD4-PE40 immunotoxins that are not analogous to the instant invention as they do not target only infected cells. Hence any "results" based on the Application of said immunotoxin would not have any bearing on the perceived efficacy of immunotoxin based on the combination of the cited references which target only infected cells.

With regards to Applicants assertion that the failure of CD4-PE immunotoxins to live up to expectations and hence would remove the motivation provided by Matsushita, said assertions are deemed unpersuasive. "Diminished enthusiasm" for a failed treatment modality is common response especially when the expectations of said modality was high. Moreover, the failure of a non-analogous immunotoxin, while it may have been discouraging would not necessarily remove the motivation provided by Matsushita, especially when his immunotoxin (which is analogous to the instant invention) was disclosed to have efficacy. Moreover, the "long felt need" for AIDS treatments was met by the teachings of Matsushita and would provide additional motivation for the skilled artisan to further refine the teachings of Matsushita.

As outlined previously, Matsushita et al. disclose anti-pg120 immunotoxins comprising the 0.5β antibody coupled to the *Pseudomonas* exotoxin (see abstract). Matsushita et al. differs from the instant invention in that they don't disclose the use of the 3B3 antibody or the use of altered PE40. Barbas et al. disclose a human antibody to gp120 (3B3) with broad strain cross-

reactivity (see page 3812-3813). Pastan et al. disclose modifications of the carboxyl terminus of the PE molecule resulting in increased cytotoxicity (see abstract and column 3, line 27 to column 4, line 10). Given that Matsushita et al. suggest the use of an antibody that is broadly reactive with a number of HIV isolates (see page 200), it would have been obvious for one of ordinary skill in the art to use the 3B3 antibody in the immunotoxin disclosed by Matsushita et al. Moreover, it would a have been equally obvious for one of ordinary skill to incorporate the PE modifications disclosed by Pastan et al. in order to take advantage of the resulting increase in cytotoxicity. It should be noted that while the incorporation of immunotoxins in kits is not explicitly disclosed by Matsushita et al., said incorporation would have been obvious to one of ordinary skill in the art in order to reduce cost and ease preparation time.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ROBERT A. ZEMAN
PATENT EXAMINER

October 5, 2005